THE TEMPORAL ARCHITECTURE OF COLLAPSE

A Three-Phase Theory of Alzheimer's Disease — From Bioenergetic Ignition in the Locus Coeruleus to Synaptic Disintegration of the Perineuronal Net

Bioenergetic Ignition · The Locus Coeruleus Bridge · The Microglial Bridgehead
The Proteolytic Turn · Synaptic Disintegration

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Capstone synthesis of the Collapse trilogy — Bioenergetic Collapse, Homeostatic Microglial Collapse, and Convergent Synaptic Collapse — with the Locus Coeruleus Bridge and the Proteolytic Turn, and companion to The Homeostatic–Matrix–Synaptic Axis.

Contents

Abstract

Alzheimer's disease is not an event. It is a process that occupies the better part of a human life — a slow structural failure that begins in the third decade, in a single small nucleus of the brainstem, and completes itself in the eighth decade, in the inhibitory scaffolding of the cortex, fifty years and twelve centimetres away. The dominant theoretical frameworks of the past four decades have, almost without exception, been frameworks of *substance* rather than of *time*: they ask which molecule is primary — amyloid, tau, the activated microglion, the failing mitochondrion — and they arrange the answer as a cascade in which one species begets the next. This paper advances a different organizing principle. It proposes that the deepest structure of Alzheimer's disease is *temporal*: that the disease is a stereotyped three-phase progression with two mechanistically specified transitions between the phases, and that the identity of the "primary" molecule is not fixed but changes as the disease moves through time, because each phase is load-bearing on a different substrate, a different cell type, and a different decade of life.

We name the three phases **Bioenergetic Ignition** (Phase I, decades 3–5), the **Homeostatic Microglial Bridgehead** (Phase II, decades 6–7), and **Synaptic Disintegration** (Phase III, decade 8 and beyond). Phase I is the decades-long, clinically silent erosion of mitochondrial and autophagy–lysosomal quality control in the locus coeruleus and the brainstem aminergic nuclei — the most metabolically extravagant and earliest-failing neurons in the human brain — driven by PARP-1 hyperactivation, NAD+ depletion, and the obstruction of mitochondrial protein import. Phase II is the collapse of the TGF-β/SMAD-maintained homeostatic microglial state in the hippocampus, which converts the brain's resident immune cells from custodians into a population whose every protective withdrawal is simultaneously a destructive act. Phase III is the digestion of the perineuronal net surrounding the parvalbumin-positive fast-spiking interneuron — the structural event that releases inhibitory control, collapses excitatory–inhibitory balance, and produces the network failure experienced as dementia.

The intellectual core of the theory is not the three phases, which the field has glimpsed in pieces, but the two *bridges* that connect them. The transition from Phase I to Phase II is executed by the locus coeruleus itself, whose ascending axons deliver, along a single anatomical substrate, both the withdrawal of noradrenergic suppression of microglia and the trans-synaptic seeding of templated tau — the same projection that regulates the forebrain becoming the projection that poisons it. The transition from Phase II to Phase III is executed by what we term the **Proteolytic Turn**: the convergence of a lipid-gridlock-driven proteolytic switch (NLRP3 IL-1β MMP-9), iron liberated from ferroptotic oligodendrocytes catalysing Fenton chemistry on the matrix, and complement priming of the perineuronal sheath, all three arms meeting on the aggrecan–brevican coat of the parvalbumin interneuron. A theory of Alzheimer's that names its transitions is a theory that can be falsified, staged, and interrupted; a cascade that only names its endpoints cannot.

Beneath the temporal sequence runs a single unifying current. The three phases are not three diseases but three expressions of the age-dependent collapse of one homeostatic system, maintained throughout by TGF-β/SMAD signalling, pivoting at each phase through the receptor TREM2, and converging at every phase on the same anatomical address — the perisomatic zone of the parvalbumin interneuron. This is why cognitive resilience, when it occurs, requires the *joint* preservation of homeostatic microglia, intact matrix, and competent inhibitory synapses, and is never bought by the preservation of any one layer alone. We close by drawing the therapeutic consequence that follows inexorably from a temporal theory: that the repeated failure of single-target monotherapies is not bad luck but a structural prediction, because a drug aimed at one phase's molecule arrives, in most trials, a decade or more after that phase has closed. One note on scope governs everything above: the disease described here is Alzheimer's as *biologically* defined — amyloid-positive, tau-positive, of typical topography — which is a minority of dementia as clinically encountered, most plausibly ten to fifteen per cent of it.

I. The Problem of Time

The field's blind spot

For nearly forty years the intellectual energy of Alzheimer's research has been spent adjudicating a question of priority. Is the disease caused by amyloid-β, deposited as the plaques Alois Alzheimer saw in 1906? By the hyperphosphorylated tau of the neurofibrillary tangle? By the activated microglion, the failing mitochondrion, the leaking vessel, the reactivated virus? Each candidate has assembled a literature, a community, and a therapeutic programme around itself, and each has organized its evidence into the same rhetorical shape: a cascade, in which a primary insult begets a secondary one, which begets a tertiary, terminating in the death of neurons and the loss of mind. The amyloid cascade hypothesis is the most famous example, but it is not unusual in form. Every major framework in the field is a cascade. They differ only in what they place at the top.

What unites these frameworks is more revealing than what divides them. They are all theories of *substance* — theories about which molecular species is causally primary — and they are almost all silent about *time*. They treat the half-century over which Alzheimer's disease actually unfolds as an inconvenience to be compressed into an arrow between two boxes, rather than as the phenomenon's most important structural feature. This is the field's central blind spot. A disease that takes fifty years to complete is not well described by asking which of its molecules came first, any more than the history of a fifty-year war is well described by naming the calibre of the first bullet. The right question is not *what* but *when*: which process is load-bearing in which decade, on which substrate, in which cell.

A half-century, not a moment

The clinical and neuropathological data have been telling us this for a generation, if quietly. Braak and Del Tredici's staging of pretangle tau places its earliest deposits not in the entorhinal cortex but in the locus coeruleus, and places them not in old age but in early adulthood — pretangle material is detectable in the brainstem of individuals in their twenties and thirties. Cerebrospinal-fluid Aβ42 begins its decline roughly two decades before the first subjective complaint of forgetfulness. Amyloid positron-emission tomography turns positive a decade to fifteen years before diagnosis; plasma phospho-tau217 inflects years before that diagnosis again; neurofilament light chain rises across the entire span and never plateaus. Read together, these biomarkers do not describe a moment of onset. They describe a slow front of failure that crosses the brain over five decades, from brainstem to cortex, from metabolism to architecture, from the silent to the catastrophic.

The temporal facts are therefore not in dispute. What has been missing is a theory that takes them as its skeleton rather than its footnote — a theory in which the passage of time is the organizing variable and the changing identity of the "primary" molecule is a consequence of that passage rather than an embarrassment to be argued away. The reason such a theory has been slow to assemble is partly disciplinary: the people who study brainstem catecholaminergic neurons in the third decade of life are not, in general, the people who study cortical perineuronal nets in the eighth, and the two literatures have grown up speaking different languages about what they each, unknowingly, call the same disease at different ages.

Thesis

This paper proposes that Alzheimer's disease has a definite temporal architecture: three phases, each load-bearing on a distinct substrate and a distinct decade, connected by two mechanistically specified transitions. We state the architecture plainly here and defend each element in the sections that follow.

Before doing so, the scope of the claim must be fixed, because the word "Alzheimer's" is used in two incompatible senses in the literature and the difference decides what this paper may be said to have described. The architecture below is an account of Alzheimer's disease *biologically defined* — amyloid-positive and tau-positive, of typical topography — and not of dementia as it presents in clinic. The two are not the same population. Most demented brains carry more than one pathology at autopsy, and pure or near-pure Alzheimer's is a minority of dementia: between three and twenty-two per cent depending on how many pathologies a study scores and how strictly topography is judged, most plausibly ten to fifteen. Every claim in this paper should be read as a claim about that entity — what the programme's own routing analysis calls *Route 1* — and not about dementia as encountered. The scope note in §II states what that restriction costs.

Phase I — Bioenergetic Ignition (decades 3–5). The locus coeruleus and the brainstem aminergic nuclei, the most metabolically demanding neurons in the brain, undergo a decades-long, clinically silent erosion of mitochondrial and autophagy–lysosomal quality control. PARP-1 hyperactivation and NAD+ depletion, compounded by obstruction of mitochondrial protein import, push these cells past the point at which damaged organelles can be cleared.

The Locus Coeruleus Bridge (Phase I II). The same locus-coeruleus axons that have begun to fail deliver, across the forebrain, both the withdrawal of noradrenergic suppression of microglia and the trans-synaptic seeding of templated tau. One projection executes both the loss of regulation and the delivery of pathology.

Phase II — The Homeostatic Microglial Bridgehead (decades 6–7). In the hippocampus, the TGF-β/SMAD-maintained homeostatic microglial signature collapses. The resident immune cells enter post-homeostatic states whose protective withdrawal and destructive attack are no longer separable.

The Proteolytic Turn (Phase II III). Three converging arms — a lipid-driven proteolytic switch, iron-catalysed Fenton chemistry, and complement priming — meet on the perineuronal net of the parvalbumin interneuron, turning a cytokine-secreting microglial population into a matrix-digesting one.

Phase III — Synaptic Disintegration (decade 8+). The perineuronal net is digested, the parvalbumin interneuron loses its protective coat and its inhibitory competence, excitatory–inhibitory balance collapses, and the network failure we call dementia ensues.

Each claim is independently sourced in the Collapse trilogy and its companion analyses; the contribution of the present synthesis is to assemble them into a single, falsifiable temporal structure and to draw out what that structure implies — for resilience, for biomarkers, and above all for treatment.

II. The Architecture in Brief

Before defending the architecture in detail it is worth seeing it whole. The disease may be read as five stations along a single front of failure that crosses the brain over half a century. Two of the stations are phases — extended epochs of pathology resident in a particular cell population — and two are bridges, the specified mechanisms by which the front advances from one resident population to the next. The fifth is the terminus.

Phase I — Bioenergetic Ignition. *Decades 3–5. Locus coeruleus and brainstem aminergic nuclei.* The load-bearing failure is metabolic and custodial: PARP-1/NAD+ depletion and the breakdown of mitophagy and autolysosomal clearance. Clinically silent; its only outward signs are the prodromal disturbances of sleep, mood, and arousal that precede memory loss by decades.

The Locus Coeruleus Bridge. *The ascending LC projection.* Two arms — noradrenergic brake withdrawal and trans-synaptic tau seeding — carried along the same axons to the hippocampus.

Phase II — The Microglial Bridgehead. *Decades 6–7. Hippocampus.* The load-bearing failure is the collapse of homeostatic microglial identity. Attack and failure become a single event; the cell that should protect the synapse begins, by the same action, to strip it.

The Proteolytic Turn. *The aggrecan–brevican sheath of the parvalbumin interneuron.* Three arms — proteolytic switch, iron liberation, complement priming — converging on the matrix.

Phase III — Synaptic Disintegration. *Decade 8 and beyond. Cortical and hippocampal parvalbumin interneurons and their perineuronal nets.* The load-bearing failure is structural and electrical: matrix digestion, loss of inhibitory tone, excitatory–inhibitory collapse, and the self-sustaining circuit failure that presents as dementia.

The architecture has three properties worth stating in advance. It is *anatomically directional* — the front moves from brainstem to limbic system to cortex, in the same rostral order that Braak staging has documented for tau. It is *substrate-shifting* — the primary lesion is metabolic in Phase I, immunological in Phase II, and structural in Phase III, which is precisely why no single-substrate theory has ever fit the whole disease. And it is *bridged* — the transitions are not gaps to be waved across but mechanisms in their own right, each with named molecular arms and a named anatomical substrate. It is the bridges, more than the phases, that make the theory a theory.

A note on which disease this describes

The architecture is stated above without qualification, and it should not be read that way. Two filters stand between it and dementia as a clinician meets it, and both are large. The first is co-pathology: most demented brains carry more than one lesion at autopsy, and the fraction of cases in which Alzheimer pathology runs alone falls monotonically as more pathologies are scored — from 30 per cent of dementia on a three-pathology panel to 3.13 per cent on a full one, which means these are not competing measurements but one disease seen through panels of different width. The second is topography: roughly three quarters of autopsy-confirmed cases follow the typical Braak distribution, and only about a third of tau-PET trajectories are Braak-like. Under the strictest reading — pure pathology, conforming topography, all three phases as specified — the architecture describes something between 3 and 22 per cent of dementia, most plausibly 10 to 15.

Three consequences follow, and each is a restriction on what the sections below may be taken to have shown. **Entry is near-universal.** Abnormal tau is present in 99.6 per cent of adult brains, and primary age-related tauopathy — brainstem and medial temporal tau without significant amyloid — carries a dementia rate of 1.4 per cent. Phase I is therefore better stated as *the substrate on which the disease is built* than as the event that starts it; what converts an ignition into a progression is not specified here, and is this programme's largest open question. **Exit is not guaranteed by traversal.** Between 12 and 22 per cent of individuals at Braak V–VI are not demented. Phase III produces the *substrate* of dementia; whether it produces the *syndrome* is set by resilience factors this architecture does not model. **The remainder are routes, not attrition.** The cases these filters exclude have dementia and went somewhere — limbic-predominant and hippocampal-sparing topographies, LATE-NC, Lewy and vascular co-pathology. This paper does not describe them, and the corpus does not yet either. See [[coverage-fraction]].

A note on what can be measured

Stated in advance, because it bears on how every claim below should be read: **two of these three phases currently have no human in vivo instrument, and this thesis does not treat their resistance to refutation as evidence for them.**

Phase I is anchored in post-mortem tissue, not in imaging. Braak's series is strong and is what the phase rests on — of 42 brains aged 4 to 29, 38 carried pretangle tau, and in 19 of 22 the material was confined to the coeruleus/subcoeruleus complex; in 2,332 unselected brains, 58 carried subcortical tau predominantly in the coeruleus with no cortical tau anywhere. But the locus coeruleus is a thread 2 to 2.5 mm across, harmonised tau-PET effective resolution is 6 to 8 mm, and the dominant tracer binds off-target to the very neuromelanin that defines the nucleus. No published study quantifies tau-PET signal within a coerulean region of interest, and standard T1 imaging shows no contrast there at all. The in vivo literature is accordingly cited here as *consistent and suggestive, thinly longitudinal* — one study carries longitudinal coerulean imaging together with longitudinal tau-PET, over a window of under three years — and never as confirmation. It follows that the absence of the coeruleus from data-driven staging models is not evidence against this phase; no such model has ever included a brainstem region.

Phase III is a hypothesis with a named measurement gap. There is no technique for imaging perineuronal nets in the living human brain. The phase rests on post-mortem tissue and animal models, and it is doubly qualified: the programme's own blind audit found parvalbumin involvement to be late and functional, with somatostatin interneurons preceding it, so the ordering claim survives while the identity of the terminal cell does not.

Phase II is the well-instrumented one — MRI, tau-PET, cerebrospinal fluid and plasma all reach it. It is therefore also the phase most exposed to contradiction, and the reader should weigh the three phases accordingly rather than uniformly. See [[phase-measurability]].

III. Phase I Bioenergetic Ignition

The locus coeruleus as first to fall

If one asks which neuron in the human brain is the first to show Alzheimer-type pathology, the neuropathological answer has been known for over a decade and is not the one the amyloid literature would predict. It is not a cortical pyramidal cell. It is the noradrenergic neuron of the locus coeruleus, a nucleus of roughly fifty thousand cells in the dorsal pons whose pretangle tau deposits, as documented by Braak and Del Tredici, appear in early adulthood — before any cortical involvement, before any plaque, before any symptom. The locus coeruleus is, in the most literal temporal sense, where Alzheimer's disease begins.

Why there? The answer is bioenergetic. The locus-coeruleus neuron is among the most metabolically extravagant cells in the brain. It is autonomously pacemaking, firing tonically throughout waking life; it sustains long, thin, unmyelinated or sparsely myelinated axons, projecting through varicose, branching fibres that reach virtually the entire forebrain; and it must maintain catecholamine synthesis, a chemistry that is itself a source of oxidative load. A cell with this profile lives perpetually close to the ceiling of its mitochondrial capacity. It has, in effect, no metabolic reserve to spend on the slow accumulation of unrepaired damage — and so it is the cell in which the universal, age-dependent erosion of cellular quality control first crosses the threshold from compensated to decompensated.

The quality-control machinery

The substrate of Phase I is not a protein but a process: the failure of the machinery by which a neuron disposes of its own damaged components. Two genetic anchors of late-onset Alzheimer's disease bracket this machinery at its two ends. At the formation end sits *BIN1* — the second-strongest common genetic risk locus for the disease — which, through its partnership with the ESCRT-III machinery and dynamin-2, governs the closure of the autophagosome around its cargo. At the degradation end sits presenilin, whose role in lysosomal acidification is independent of its more famous role in γ-secretase: without proper acidification the autolysosome cannot activate its hydrolytic enzymes. A lesion at either end produces the same outcome — the accumulation of undegraded autophagic cargo, including damaged mitochondria and intraneuronal Aβ — and it is this convergence, formation-failure and degradation-failure yielding one phenotype, that identifies quality control rather than any single protein as the true Phase I lesion.

The mitochondrial arm of this machinery is the PINK1/Parkin mitophagy pathway, which recognizes a depolarized mitochondrion, ubiquitinates its outer membrane, and recruits the autophagy adapters that consign it to destruction. This system is doubly defeated in the ageing neuron. NAD+, the central currency of mitochondrial metabolism, declines with age and is further depleted by the hyperactivation of PARP-1 in response to accumulating DNA damage — a depletion that starves the sirtuins and cripples mitochondrial biogenesis. And the import of nuclear-encoded proteins into the mitochondrion, the process by which the organelle's proteome is continually replaced, is physically obstructed when Aβ binds the import channel TOM40 (as α-synuclein binds TOM20 in the parallel pathology of Parkinson's disease). A mitochondrion that cannot import new proteins cannot be repaired; a neuron that cannot clear the mitochondrion it can no longer repair accumulates a population of failing organelles whose reactive-oxygen output gates the NLRP3 inflammasome and primes the inflammatory effector arm that will matter in Phase II. The terminal morphology of this process — the flower-like neuron swollen with expanded autolysosomes that Nixon and colleagues named PANTHOS — is, on this reading, not a curiosity but the visible endpoint of Phase I, and the plaque that forms when such a neuron ruptures is its gravestone rather than its cause.

Why ignition is silent

The defining clinical feature of Phase I is that it produces no dementia. For two to three decades the locus coeruleus and its aminergic neighbours degrade in near-silence, and the only outward signs are the disturbances one would predict from the slow loss of noradrenergic, serotonergic, and related tone: disrupted sleep architecture, blunted arousal, depressed mood, autonomic instability — the prodromal symptoms that epidemiology has long linked to later dementia without being able to explain the link. The silence is mechanistically important, not incidental. It means that by the time memory fails, the disease is not beginning; it is entering its third act. It means that the therapeutic window for the upstream lesion opens decades before any patient presents. And it means that the transition out of Phase I — the moment the brainstem lesion stops being a private metabolic affair of fifty thousand cells and becomes a forebrain disease — requires its own explanation. That explanation is the first bridge.

IV. The First Bridge The Locus Coeruleus

The locus coeruleus does not merely begin the disease and then wait for the cortex to catch up. It is the active vector of the transition. The paper that specifies this transition — *The Locus Coeruleus Bridge* — makes a claim of unusual structural elegance: that the very anatomy which makes the nucleus a

master regulator of the forebrain is the anatomy that makes it the forebrain's instrument of harm. The transition runs along two arms, and the arms share a single substrate, the ascending LC projection.

Arm one — withdrawal of the noradrenergic brake

The locus coeruleus supplies noradrenaline to the entire forebrain through volume transmission: its varicose axonal boutons release transmitter not into discrete synapses but diffusely into the parenchyma, bathing wide territories in noradrenergic tone. Among the cells listening are the microglia, which express the β2-adrenergic receptor. Through Gs-coupled signalling — cAMP, protein kinase A, and the inhibitory phosphorylation of NF-κB — noradrenaline tonically suppresses the microglial transcription of pro-inflammatory cytokines. Noradrenergic tone is, in effect, a standing brake on microglial activation, one of several tonic brakes (alongside the CX3CR1–fractalkine and CD200–CD200R axes and the TGF-β/SMAD programme itself) that together hold the resident immune cell in its homeostatic state.

When the locus coeruleus degenerates in Phase I, this brake is released. The loss is not local: because LC projections are diffuse and brain-wide, the withdrawal of noradrenergic suppression raises the inflammatory set-point of microglia across the forebrain, and it does so preferentially where LC innervation is densest. The hippocampus, richly innervated by the coeruleus, is among the first territories to feel the brake come off. Heneka and colleagues demonstrated the principle directly: lesioning the locus coeruleus accelerates amyloid pathology and exaggerates the inflammatory response in animal models, exactly as the withdrawal-of-suppression account predicts.

Arm two — trans-synaptic tau seeding

The second arm uses the same axons for a different cargo. The pretangle tau that has accumulated in locus-coeruleus neurons since early adulthood is not inert. It is competent to seed: released from the presynaptic terminal, internalized by the postsynaptic neuron through LRP1 and heparan-sulfate-proteoglycan-mediated endocytosis, it templates the misfolding of the host's native tau, generating new propagation-competent seeds that move on, synapse by synapse, along the projection. The locus coeruleus, with its vast and branching efferent tree, is an almost ideal distributor for such a templated agent, and the hippocampus — densely innervated, and richly endowed with the LRP1 and heparan-sulfate receptors that mediate uptake — is an almost ideal recipient.

One projection, two failures

The two arms are not independent processes that happen to co-occur. They are carried by one anatomical substrate to one destination, and they arrive together. The hippocampus receives, through the same axonal arbor and in the same epoch, both the cessation of the noradrenergic brake on its microglia and a stream of templated tau seeds. The convergence is the point. As the bridge paper puts it, the locus coeruleus is in functional terms the forebrain's noradrenergic regulator and in pathological terms the forebrain's tau-seed delivery system, and the same axons execute both roles — so that their failure is, in a single stroke, both the loss of regulation and the delivery of pathology. This dual-pressure arrival on the hippocampus is what converts a brainstem metabolic disease into a limbic immune disease. It is the hand-off from Phase I to Phase II.

V. Phase II The Microglial Bridgehead

Collapse of the homeostatic signature

The microglion in its healthy state is defined by a transcriptional signature — P2RY12, TMEM119, CX3CR1, SALL1, HEXB, and their companions — that Butovsky and colleagues showed to be maintained by TGF-β/SMAD signalling. This signature is not a label; it is a behavioural programme. The homeostatic microglion surveys, supports, and prunes with restraint, holding the parenchyma in equilibrium. Phase II is the collapse of this programme. Under the chronic oxidative and metabolic stress that arrives with the released noradrenergic brake, the tau seeds, and the cell's own ageing, SMAD signalling is dysregulated, the inhibitory feedback of SMAD7 rises, and the homeostatic markers are lost. The cell exits its homeostatic state — and, crucially, the exit is the disease, not the level of amyloid or tau the cell is responding to.

The decisive evidence for this ordering comes from the neuropathology of resilience. De Vries and colleagues documented cognitively intact individuals who carry amyloid and tau burdens fully in the Alzheimer range and yet do not have dementia — and what distinguishes their brains is not less pathology but preserved homeostatic microglia and intact perineuronal nets. Homeostatic preservation, not pathology absence, is the substrate of resilience. This single finding reorders the causal hierarchy of the entire disease: it places the microglial state, not the protein burden, on the critical path to cognitive failure.

Post-homeostatic trajectories

Having left the homeostatic state, the microglion does not enter a single "activated" state but a family of post-homeostatic trajectories, each described by a distinct literature and each converging on the same end. The disease-associated microglia (DAM) of Keren-Shaul and Amit pass through a TREM2-independent first stage into a TREM2-dependent second stage marked by APOE, CST7, the cathepsins, LPL, SPP1, and ITGAX. The lipid-droplet-accumulating microglia (LDAM) of Marschallinger gorge on myelin debris until their cytoplasm gridlocks with lipid, a state that is at once metabolically senescent and primed for inflammasome assembly. The dystrophic microglia of Streit, driven by iron and ferritin accumulation, fragment and bead toward terminal senescence in the company of pre-tangle tau. The receptor TREM2 sits at the collision point of these trajectories, coupling lipid and apolipoprotein sensing through DAP12, SYK, and the PI3K–AKT–mTOR axis to the cell's phagocytic and metabolic competence — which is why it recurs at every level of the disease.

Attack and failure as one event

The deepest insight of the Phase II thesis is that the long-running debate over whether microglia in Alzheimer's are harmful (attacking synapses) or merely insufficient (failing to clear pathology) is a false dichotomy resting on a hidden assumption — that attack and failure are different acts. At the perineuronal net they are the same act. When a post-homeostatic microglion digests the aggrecan and tenascin-R coat of a parvalbumin interneuron, it is at one and the same moment destroying a protective structure and withdrawing a protective service. There is no version of the event that is purely one or the other. The effector arms that execute it — complement C1q and C3 tagging followed by CR3-mediated engulfment; the cell-autonomous C4d–LilrB2 pathway of Werneburg and Shatz; the matrix metalloproteinases and ADAMTS proteases; the cathepsins — are the same arms that, deployed with restraint in the homeostatic state, maintain the very structures they now dismantle. Phase II is therefore best understood not as the brain acquiring a harmful cell type but as losing the governor on a cell type it has always possessed. The hippocampus is where this loss first consolidates into a self-sustaining lesion — the bridgehead from which the disease will move on the cortex. How it moves is the second bridge.

VI. The Second Bridge The Proteolytic Turn

The transition from Phase II to Phase III was, before its specification, the most under-described boundary in the whole architecture — the field could see microglial collapse on one side and

synaptic loss on the other, but the mechanism that joined them was a gap. *The Proteolytic Turn* fills the gap with the same rigour the Locus Coeruleus Bridge brought to the first transition, and it finds that this boundary, unlike the first, requires three arms rather than two. The reason is that the target is no longer a cell but a structure — the perineuronal net — and a structure as chemically heterogeneous as the aggrecan–brevican sheath can be attacked along several independent chemistries at once.

Arm one — the proteolytic switch

The first arm is a change in the microglial secretory programme itself. The lipid-laden post-homeostatic microglion of late Phase II uses its accumulated lipid droplets as assembly platforms for the NLRP3 inflammasome, while the same lipid burden destabilizes lysosomal membranes and raises mitochondrial reactive-oxygen output — two further NLRP3 triggers. Activated NLRP3 licenses caspase-1 to cleave pro-IL-1β into its mature form; IL-1β then acts back on the microglion, through NF-κB and AP-1, to drive transcription of MMP-9, MMP-3, and ADAMTS-4/5. The cell that spent Phase II secreting cytokines now, over months to years, becomes a cell that secretes matrix proteases. This is the proteolytic switch — the conversion of an inflammatory phenotype into a frankly digestive one — and it is, in Crapser's work, the proximate microglial cause of perineuronal-net loss in the Alzheimer brain.

Arm two — iron liberation and Fenton catalysis

The second arm is inorganic. The oligodendrocytes that die by ferroptosis in Phase II do not die cleanly; ferroptotic death dismantles membranes and releases redox-active iron — Fe2+ from ferritin, from heme, from iron–sulfur clusters — into the surrounding parenchyma. The perineuronal net is an avid iron sink: the sulfate and carboxylate groups of its chondroitin-sulfate and heparan-sulfate glycosaminoglycans bind iron tightly. An iron-loaded net is a substrate for Fenton chemistry, in which Fe2+ and hydrogen peroxide generate the hydroxyl radical — a species so reactive that its diffusion radius is roughly a nanometre, meaning it damages whatever holds the iron that made it. The radical fragments the proteoglycan core and its side chains, and the fragmentation is self-amplifying: oxidatively damaged aggrecan is more susceptible to the MMP and ADAMTS cleavage of arm one, and each smaller fragment binds iron more densely per unit area, sharpening the next round of catalysis. Arms one and two are thus not parallel but multiplicative — enzymatic and inorganic degradation each making the matrix a better target for the other. The labile-iron biology that Ayton and Bush placed at the centre of Alzheimer's progression is, in this account, the chemistry of the second bridge.

Arm three — complement priming

The third arm marks the matrix for removal. Post-homeostatic microglia deposit C1q on synapses and on the perineuronal net, whose aggrecan and brevican epitopes are accessible to it; C1q activates the classical cascade, C4 is cleaved, and C4d "eat-me" opsonins are laid down on the sheath. C4d-opsonized matrix is then recognized by CR3 on the microglion, licensing the phagocytic stripping of the net. Critically, this tagging is not uniform — it follows the geography of prior Phase II damage, so that the regions where pyramidal-neuron quality control failed earliest are the regions where the matrix is marked for digestion first. Hong, Stevens, and colleagues showed that complement and microglia mediate early synapse loss in Alzheimer models independently of plaque burden, and that genetic removal of C1q or C3 is protective — the clearest demonstration that this arm is causal rather than reactive.

The perineuronal net as the second bridgehead

The three arms meet on one structure: the aggrecan–brevican coat of the parvalbumin-positive fast-spiking interneuron, densest in cortical layers III–IV, in hippocampal CA1, and in the basolateral amygdala. When that coat is digested, the consequence is not merely the loss of a structure but the entry of its host cell into a new and self-sustaining trajectory. The Proteolytic Turn paper states the matter with precision: the parvalbumin interneuron is the Phase III bridgehead in the same sense that the hippocampus was the Phase II bridgehead — the cellular environment in which converging upstream pressures consolidate into a pathology that no longer needs further input from earlier phases to advance, because the loss of the protective envelope creates conditions under which the neuron's own metabolic demand exceeds its substrate supply and it enters an oxidative-substrate-failure trajectory that does not spontaneously reverse. The bridge does not merely deliver the disease to Phase III; it ignites it.

VII. Phase III Synaptic Disintegration

The parvalbumin interneuron as final substrate

Every thread of the architecture terminates on one cell. The parvalbumin-positive fast-spiking interneuron is the metronome of cortical computation: it provides the perisomatic inhibition that paces pyramidal-cell firing and that generates the gamma-frequency rhythms on which working memory and attention depend. It is also, by virtue of its extraordinary firing rate, among the most metabolically demanding and most oxidatively exposed neurons in the cortex — which is why it depends on the perineuronal net not only as a structural scaffold but as a protective buffer, an ion-exchange and antioxidant envelope without which its own activity would poison it. The digestion of that net in the Proteolytic Turn therefore does not merely disinhibit the cortex; it strips the most vulnerable cortical neuron of the one structure that allowed it to survive its own metabolism. Phase III is the consequence: the loss of inhibitory tone, the collapse of excitatory–inhibitory balance, the degradation of gamma rhythms, and the network failure experienced as dementia.

Endosomal and excitatory failure

The synaptic thesis assembles eight independent frameworks onto this substrate, and they enrich the picture in two directions. The first is endosomal. Small's retromer work and Ramsden's lipid-peroxidation work converge on a failure of endosomal trafficking — the retromer hub (VPS35, VPS26, VPS29, SORLA) jams, ApoER2–Dab1 recycling is arrested by reactive lipid aldehydes generated preferentially in APOE4 carriers, and Gouras's intraneuronal Aβ accumulates in the multivesicular bodies and late endosomes of cells whose trafficking and clearance have failed. This is the same quality-control collapse that defined Phase I, now playing out in cortical and entorhinal pyramidal neurons — a reminder that the phases are not different diseases but the same lesion advancing through successive cell populations. The second direction is excitatory. Moosmann and Rappoport invert the canonical dogma: hyperphosphorylated tau and accumulating Aβ are read not as primary drivers but as maladaptive compensatory responses to a primary insufficiency of glutamatergic, NMDA-receptor-mediated signalling. On this view the proteins the field has spent forty years attacking are, in part, the scar tissue of an earlier wound.

The self-sustaining loop

What makes Phase III terminal is that it closes a loop. The loss of perineuronal nets disinhibits the cortex; disinhibition raises excitatory load and oxidative stress on already-vulnerable neurons; that stress drives further microglial activation and further matrix digestion; and the cycle compounds. The Spectrum of Collapse analysis frames this as the crossing from the intrinsic pole of cell death — the slow, aging-linked quality-control failures of Phase I, clinically silent and shared with normal ageing — to the extrinsic pole, the multi-modal death (excitotoxic, ferroptotic, phagoptotic, necroptotic) to which a parvalbumin interneuron stripped of its net becomes exposed. The decades of intrinsic erosion are survivable and common; it is the crossing to extrinsic, circuit-level collapse, centred on the perineuronal net, that is the defining disease event. This is why dementia, when it finally arrives, arrives comparatively fast: the patient has not just reached the end of a slope but tipped over a self-reinforcing edge.

VIII. The Convergence Beneath the Sequence

One system, failing in sequence

A reader who has followed the architecture to this point may object that a three-phase sequence with two bridges is still, in the end, a cascade — more carefully staged than its predecessors, but a chain of causes nonetheless. The objection is worth meeting directly, because the answer is the theory's deepest claim. The three phases are not three diseases linked by transitions. They are three expressions, resident in three successive cell populations, of the age-dependent collapse of a *single homeostatic system*. The temporal sequence is real, but it is the sequence in which one system fails across the brain, not a relay of distinct pathologies handing off a baton.

Shared substrate, signal, and pivot

Three observations establish the underlying unity, and they are the load-bearing findings of the Homeostatic–Matrix–Synaptic synthesis that runs beneath this temporal account. First, the three phases share an *anatomical substrate*: the perisomatic zone of the parvalbumin interneuron is the one address at which all three frameworks make coincident predictions, and the loss of parvalbumin synaptic coverage is the common final pathway through which each derives cognitive failure. Second, they share an *upstream signal*: TGF-β/SMAD signalling maintains the homeostatic microglial state of Phase II, but it is also held in latent form within the perineuronal matrix of Phase III, and it restrains the developmental complement-pruning programmes that execute synaptic loss — so that a single signalling collapse produces microglial, matrix, and synaptic pathology at once. Third, they share a *molecular pivot*: TREM2 gates the DAM transition in the microglial frame, is engaged by the chondroitin-sulfate fragments released during matrix degradation in the perineuronal frame, and mediates the lipid-raft and endosomal engagement that links trafficking failure to microglial output in the synaptic frame. One substrate, one signal, one pivot, three times over: the recurrence is the evidence that we are watching one system, not three.

Resilience as triple preservation

The unity makes a sharp, counter-intuitive prediction about resilience, and the prediction is already partly confirmed. If the three phases were independent, cognitive resilience could be bought by blocking any one of them. Because they are three faces of one system, resilience requires the *joint* preservation of all three layers — homeostatic microglia bearing the Butovsky signature, intact aggrecan/tenascin-R matrices around parvalbumin interneurons, and competent parvalbumin inhibitory synapses — and no single layer's preservation suffices. The resilient brains documented by de Vries are resilient not because they lack amyloid or tau but because all three layers are held intact together. This is the theoretical reason that the disease's transition from mild cognitive impairment to dementia behaves like the crossing of a threshold rather than the descent of a slope: the threshold is the point at which the feed-forward loop between the three layers becomes self-sustaining, reversible by homeostatic restoration before the crossing and not after.

IX. Cross-Sections Through the Arc

A temporal architecture invites a particular kind of companion study: take a single biological lens and draw it through all three phases, asking what that one variable is doing in each decade. Five such cross-sections have been completed, and each independently corroborates the three-phase

structure by finding that its own variable is phase-resolved — load-bearing differently in each epoch rather than uniform across the disease.

The vascular phasing

The cerebrovascular cross-section finds vascular pathology conditioning each phase in a phase-specific way. In Phase I, VCAM-1 induction at the brainstem endothelium couples systemic ageing signals to parenchymal NAD+ depletion in the locus coeruleus. In Phase II, the VCAM-1–pericyte–blood-brain-barrier axis of Yousef and Wyss-Coray admits aged-plasma toxicity to the hippocampus, gating the microglial transition. In Phase III, cerebral amyloid angiopathy and small-vessel disease convert parenchymal synaptic loss into the mixed dementia of the eighth decade. The vasculature is not a comorbidity bolted onto the disease but a substrate that anteceded the parenchymal lesion at each phase.

The genetic architecture

The genetic cross-section finds that the risk genes themselves are phase-resolved. Phase I is load-bearing on NAD+ metabolism and mitochondrial quality control (NMNAT2, SARM1, PINK1, PRKN); Phase II on the microglial and immune programme (TREM2, the complement loci, GPX4, TGFB1, SPI1); Phase III on perineuronal-net structure and the parvalbumin programme (ACAN, BCAN, TNR, MMP9, PVALB). APOE alone spans all three, through distinct mechanisms — lipid mishandling in Phase I, microglial-state collapse in Phase II, complement-mediated matrix attack in Phase III. The genetic architecture is not flat, and the failure to weight common-variant risk by phase is, on this account, a principal reason flat polygenic scores have disappointed and single-target trials have failed.

The viral trajectory

The viral cross-section treats herpes simplex and related viruses not as a competing cause but as a temporal scaffold for the host responses the other frameworks describe. Phase I sees the establishment of latency and the deposition of Aβ as the innate-immune cost of periodic subclinical reactivation; Phase II sees reactivation frequency rise with immune ageing, chronic interferon signalling helping to collapse the microglial state; Phase III sees immunosenescence unleash a final wave of reactivation on an already-undermined synaptic infrastructure. On this reading Aβ and tau are the host's distributed response to decades of antigenic load — which reframes the regression-discontinuity evidence that zoster vaccination lowers dementia risk as evidence that addressing the antigenic drive outperforms addressing the host response.

The biomarker cascade

The biomarker cross-section supplies the clinical instrument that the temporal architecture predicts must exist: a staged sequence in which each phase is marked by the *first emergence* of a new molecular signature atop the persisting earlier ones. Preclinical Phase I is the era of falling Aβ42/40 and rising sTREM2 and GFAP; prodromal Phase II is the era of the phospho-tau cascade (p-tau231 p-tau217 p-tau181) and of neurogranin and temporoparietal hypometabolism; dementia-stage Phase III is the era of sustained neurofilament light, advancing atrophy, and entrenched glial reactivity. The cascade is an active staging instrument, not a passive recorder — and its central practical lesson, that inclusion criteria must be organized by phase, is the temporal theory expressed in the grammar of trial design.

The spectrum of collapse

The cell-death cross-section organizes the modalities of neuronal death along an intrinsic–extrinsic axis and finds the axis maps onto the phases. Phase I is the pure intrinsic pole — Parthanatos, PANTHOS, Wallerian degeneration — in brainstem aminergic neurons across decades of silent erosion. Phase II is the mixed middle, intrinsic failure meeting emerging extrinsic assault in entorhinal and CA1 neurons. Phase III is the crossing to the extrinsic pole, where the denuded parvalbumin interneuron is exposed to excitotoxic, ferroptotic, phagoptotic, and necroptotic death at once. The disease, on this reading, is not a disease of ageing (the intrinsic pole) or of circuit collapse (the extrinsic pole) but of the *transition between them* — the same claim the temporal architecture makes, arrived at from the direction of death rather than of time.

X. Falsifiable Predictions

A theory earns the name by exposing itself to refutation. The temporal architecture generates predictions that are sharp, phase-resolved, and in several cases already testable with existing methods.

On resilience. Single-cell and spatial transcriptomic analysis of resilience cohorts will show *joint* preservation of all three layers — homeostatic microglia, intact perineuronal matrix, and competent parvalbumin synapses — and the preservation of any single layer alone will be found insufficient to confer resilience at Alzheimer-threshold amyloid and tau burdens.

On the first bridge. Interventions that maintain noradrenergic tone or block its withdrawal (and, separately, agents that interrupt LRP1/heparan-sulfate-mediated tau uptake) will slow the

hippocampal establishment of Phase II, and the two arms will prove separable — each partially protective alone, jointly more so.

On the second bridge. The perineuronal net will be shown to degrade through the multiplicative action of enzymatic and iron-catalysed chemistry, such that combined MMP/ADAMTS inhibition and iron chelation will preserve the net better than the sum of either alone; and genetic or pharmacological complement blockade will spare the matrix in the same regional geography in which Phase II damage occurred.

On therapy and phase. Interventions restoring upstream TGF-β/SMAD signalling will jointly preserve all three layers in animal models, whereas single-effector agents — complement inhibitors, MMP inhibitors, TREM2 agonists administered in isolation — will preserve at most one or two layers and yield only transient benefit.

On the threshold. The transition from mild cognitive impairment to dementia will be found to coincide with the point at which the three-layer feed-forward loop becomes self-sustaining, and homeostatic restoration will rescue the system before that crossing but not after — a discontinuity, not a continuum.

Each prediction is stated so that a single well-designed experiment could falsify it. That is the dividend of organizing the disease by time: the transitions, once named, become hypotheses.

XI. Therapeutic Implications The Phase-Specific Window

Why monotherapies fail

The most consequential implication of a temporal theory is also its most uncomfortable. If the load-bearing lesion changes with the decade — metabolic in Phase I, immunological in Phase II, structural in Phase III — then a drug aimed at any one phase's molecule is useful only to a patient who is in that phase. The history of Alzheimer's therapeutics is, on this reading, a history of mistimed interventions: anti-amyloid agents tested in patients whose amyloid accrual closed years before; anti-inflammatory and microglial strategies tested without regard to whether the homeostatic state had already collapsed; neuroprotective agents tested after the perineuronal net was already gone. The repeated, expensive failure of single-target monotherapies is not, on the temporal account, a run of bad luck awaiting a better molecule. It is a structural prediction of treating a substrate-shifting process as if its primary target were fixed.

Matching intervention to phase

The corollary is constructive. Each phase has a rational therapeutic logic, and they are not interchangeable. Phase I is a metabolic-and-custodial problem, and its rational interventions are upstream and presymptomatic: NAD+ restoration, PARP-1 restraint, the support of mitophagy and autolysosomal clearance — administered decades before symptoms, in individuals identified by genetic and early-biomarker risk rather than by memory complaint. Phase II is a problem of microglial identity, and its rational target is the homeostatic state itself — the restoration of TGF-β/SMAD signalling and noradrenergic tone — rather than the blunt depletion or activation of microglia wholesale. Phase III is a structural-and-electrical problem, and its window is narrow: matrix-preserving and net-stabilizing strategies must act in the interval between the initiation of perineuronal-net loss and the depletion of the parvalbumin cells the net protects, after which the substrate of rescue is simply gone.

The resilience target

The convergence beneath the sequence supplies the one target that is not phase-bound. Because resilience is the joint preservation of all three layers, and because all three are maintained by a shared upstream signal, the restoration of TGF-β/SMAD homeostatic signalling is the single intervention with a mechanistic claim to act on every phase at once — and the perineuronal net around the parvalbumin interneuron is the single most compact biomarker of whether that restoration is succeeding. A temporal theory does not merely explain why past trials failed; it nominates both an upstream target broad enough to matter across the arc and a downstream readout precise enough to measure it. The practical programme that follows is neither single-target nor indiscriminately combinatorial: it is phase-matched intervention, begun early, measured at the perineuronal net, and aimed wherever possible at the homeostatic signal the whole architecture shares.

XII. Conclusion Alzheimer's as a Process in Time

The history of Alzheimer's theory has been a long argument about substance conducted in the absence of time. Each generation has nominated its primary molecule and arranged the rest as sequelae, and each nomination has captured a real part of the disease while failing to fit the whole — because the whole is not a substance but a trajectory. The contribution of the temporal architecture is to make time the organizing variable and to discover, once it is, that the disagreements of the field largely dissolve into a question of *when*. Amyloid, tau, the activated

microglion, the failing mitochondrion, the digested matrix, the disinhibited cortex — these are not rival primary causes. They are the successive load-bearing lesions of a single front of failure that crosses the brain over fifty years, from a small nucleus in the pons in the third decade to the inhibitory architecture of the cortex in the eighth.

What turns this picture from a chronology into a theory is its two bridges. A staging scheme that only names its phases describes the disease; a theory that specifies the mechanism of each transition — the dual cargo of the locus-coeruleus projection, the three-armed proteolytic turn on the perineuronal net — can be tested, staged, and interrupted. And what turns the theory from a relay into a unity is the system beneath the sequence: one homeostatic signal, one molecular pivot, one anatomical address, failing in three successive populations, such that the cognitive resilience of the fortunate is the joint survival of all three layers and the dementia of the rest is their joint collapse.

The clinical promise of reading Alzheimer's as a process in time is finally a promise about the clock. If the disease is a fifty-year front rather than a late catastrophe, then the interval in which it can be met is not the narrow years after diagnosis but the long decades before — and the task of medicine is to learn to see the front while it is still in the brainstem, to measure it at the perineuronal net, and to act on the homeostatic signal it has been eroding all along. The disease has always been a process in time. The opportunity has always been there too. It has merely been earlier than we were looking.

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